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INFLUENCE OF ROSUVASTAIN ON THE LIPID PROFILE AND INFLAMMATORY MARKERS IN PATIENTS WITH GOUT AND ARTERIAL HYPERTENSION

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Abstract

Currently there is scarce data on lipid-lowering effects of rosuvastatin in rheumatologic pathology, moreover there are no current studies of its anti-inflammatory activity in patients with gout comorbid with arterial hypertension (AH). The purpose of this study is to investigate the lipid-lowering and anti-inflammatory effect of combination therapy with the addition of rosuvastatin in patients with gout AH. We measured and compared the level of total cholesterol, TG, LDL, VLDL, HDL, atherogenic index (AI) as well as biochemical parameters of inflammation (ESR, C-reactive protein, sialic acids, seromucoid and fibrinogen-A in 30 patients (29 male, 1 female) with gout + AH, the observation period was 43 ± 9 days. The study showed decrease in total cholesterol by 29,2% to 3,88 ± 0,78 mmol/L (p<0,0001), decrease in triglycerides by 23,91% to 1,40 [1,12 – 1,94] mmol/L (p=0,01), LDL decrease by 36,95% to 1,86 ± 0,51 mmol/L (p<0,0001), normalizing in 86,67% of patients, no effect on HDL, remaining at a level of 1,23 mmol/L and significant normalization of atherigenic index decreasing to 2,23 ± 0,83 (-30,53%, p<0,0001). Inflammation markers showed significant positive dynamics: ESR significantly decreased to 15,90 ± 9,33 mm/h (p <0,0001), the level of C-RP reached a normal value of 1,34 [0 – 6,0] mg/ml (p = 0,0007), and the concentration of sialic acid and seromucoid decreased and reached the upper limit of the norm (202,33 ± 44,0 at p=0,07 and 5,0 ± 1,25 U at p=0,004 respectively). This study shows that standard therapeutic complex with the addition of

rosuvastatin at a dose of 10 mg/day leads to a statistically significant normalization of the average levels of total cholesterol, triglycerides, LDL and VLDL and atherogenic index, causing no effect on the level of HDL. Additionally this treatment leads to significant normalization of the levels of C-RP, seromucoid and sialic acids, as well as statistically significant, but not reaching the normal values reduction of ESR and fibrinogen-A, indicating the anti-inflammatory effect of this therapeutic complex.

Keywords: hypertension, gout, lipid profile, inflammation, rosuvastatin

Introduction

Research on the possibility of using statins in systemic rheumatic diseases began in the 2000s, but quite a few of investigations are devoted to the effects of rosuvastatin in rheumatologic pathology [1, 7, 11]. Also, only a few papers describe pleiotropic effects of rosuvastatin, and data on the effectiveness of this drug in patients with gout with arterial hypertension (AH) are absent. At the same time, the literature presents data on anti-inflammatory [8, 13] and the possible anticoagulant [9, 10] effect of statins, which causes a considerable interest in the study of these effects in patients with gout, comorbid with hypertension.

Statins are long-proven leaders in their lipid-correcting effect and are currently part of the protocol therapy according to European and National guidelines for the treatment of coronary artery disease [12]. At the same time, it is recommended to use the maximum high doses of drugs, and only in the case of their intolerance or at a low risk of cardiovascular complications - the average therapeutic, for which, it should be noted, regression of atherosclerotic plaque is not proven, but its stabilization is confirmed [13]. Despite its greatest influence on the main atherogenic fractions (total cholesterol, LDL, VLDL), the effects of different statins are slightly different from each other. Thus, in the REVERSAL study (1999-2003) [4], the use of the maximum dose of atorvastatin (80 mg/day) led to lowering of LDL by 46,3% with an insignificant increase in HDL, resulting in a significant decrease in atherosclerotic plaque after 18 months of treatment by 0,4%. Interestingly, pravastatin use at a dose of 40 mg/day was accompanied by a further increase in atherosclerotic plaque (+ 2,4%), despite of 25,2% reduction in LDL. The ASTEROID study was also mainly aimed at regression of coronary atherosclerosis by taking maximal doses of rosuvastatin (40 mg/day) for 2 years. Intravascular ultrasound showed a significant decrease in the amount of atherosclerotic plaque by 1% compared toinitial values, a decrease in LDL by 53,2% and an increase in HDL by 14,7% [5]. However, the described effect of increasing HDL while taking

rosuvastatin is not present in all studies. A study by R. Rawlings et al. showed that taking 10 mg/day of rosuvastatin for 8 weeks did not lead to a significant increase in HDL [8].

In the SATURN study [3], a direct comparison was made between administration of high doses of rosuvastatin (40 mg/day) and atorvastatin (80 mg/day) in patients with coronary artery disease, which showed a more pronounced regression of atherosclerotic plaques in the rosuvastatin group (-1,22 %) against atorvastatin (-0,99%). Also, rosuvastatin caused a decrease in LDL by 48% and atorvastatin by 41%.

The efficacy of rosuvastatin as a possible hypolipidemic agent for the treatment of patients with gout comorbid with hypertension is of particular interest because the risk of atherosclerosis in these patients is extremely high [2], however, data on the lipid profile in patients with gout with concomitant arterial hypertension were not found in the literature.

A number of studies have shown the presence of a lipid-independent anti-inflammatory statin therapy effect associated with the ability of this group of drugs to block the prenylation of a large number of cytokines and other intercellular molecules, thereby inhibiting the Rho-kinase enzyme and stabilizing eNOS mRNA [8]. This, in turn, leads to a decrease in the proliferation of lymphocytes and their adhesion to the vascular wall, slowing the aging of endothelial cells by enhancing the expression of eNOS, SIRT1 and catalase [6], increasing the migration of nutrients and energy in the presence of sufficient amounts of mevalonateand, accordingly, improvement of the function of the endothelium. Thus, the data obtained convincingly prove that the most powerful and significant is the lipid-lowering effect of statin therapy, but in addition to it, biochemical mechanisms have been observed in experimental studies, which are now considered as the cause of the so-called pleiotropic effects of this group of drugs.

The purpose of the study is to study the lipid-lowering and anti-inflammatory effect of combination therapy with the addition of rosuvastatin in patients with gout and concomitant arterial hypertension.

Materials and methods

The study included 30 patients with gout with arterial hypertension. The average age of patients was 58,0 [48,0 – 72,0] years, the group included 29 men and 1 woman.All patients received standard therapy for gout and arterial hypertension, additionally receiving 10 mg of rosuvastatin per day. The observation period was 43 ± 9 days.

The study of lipid profile (total cholesterol, TG, LDL, HDL) was performed on an automatic biochemical analyzer Cobas Mira Plus (Switzerland) using "VIOLABTEST" (Czech Republic) reagent kits. Other indicators (VLDL, AI) were determined by the

calculation method. For the study of biochemical parameters of inflammation (ESR, C-reactive protein, sialic acids, seromucoid and fibrinogen-A), common methods recommended by the Ministry of Health of Ukraine for use in wide clinical practice were used. Biochemical testswere carried out at the beginning and at the end of the observation period.

The results of descriptive statistics are presented as mean ± standard deviation (for data with a normal distribution), and the median [25 - 75 quartiles] (for data with a distribution different from the normal). Testing of all samples for normality was done using the Shapiro-Wilk test. To determine the reliability of the differences between bounded samples with normal distribution and with similar dispersions, parametric methods were used (t-test), in the case of a distribution other than normal, a non-parametric Wilcoxon test was used. A value of $p \leq 0,05$ was considered statistically significant.

Results and discussion

As can be seen from Table 1, patients of the study group were characterized by an increase in total cholesterol (5,48 ± 1,00 mmol/L) and its proatherogenic fractions - TG (1,84 [1,40 – 2,31] mmol/L), LDL (2,95 ± 0,66 mmol/L) and VLDL cholesterol (0,86 [0,60 – 1,04] mmol/L), as well as decreased levels of HDL (1,23 [1,02 – 1,45] mmol/L). As a result, the atherogenic index was higher than normal and was 3,21 ± 1,13.

Table 1

Indicators of lipid metabolism in patients with gout and arterial hypertension before and after standard therapy with additional rosuvastatin

Indicator	Target levels	Before treatment (n=30)	After treatment (n=30)	Change, %	p
Total cholesterol, mmol/L	< 4,0	5,48 ± 1,0	3,88 ± 0,78	-29,20	<0,0001
Triglycerides, mmol/L	< 1,7	1,84 [1,40 – 2,31]	1,40 [1,12 – 1,94]	-23,91	0,01
β-lipoproteins, U	< 2,5	58,45 ± 17,96	45,03 ± 12,84	-22,96	<0,0001
HDL, mmol/L	< 0,8	1,23 [1,02 – 1,45]	1,23 [1,02 – 1,38]	0,00	0,54
LDL, mmol/L	<45	2,95 ± 0,66	1,86 ± 0,51	-36,95	<0,0001
VLDL, mmol/L	> 1,5	0,86 [0,60 – 1,04]	0,60 [0,56 – 0,80]	-30,23	0,005
Atherogenic Index	< 3,0	3,21 ± 1,13	2,23 ± 0,83	-30,53	<0,0001

It can be seen that protocol therapy with the addition of rosuvastatin (10 mg/day), led to the most pronounced decrease in proatherogenic fractions of cholesterol (LDL, TG and

VLDL) and total cholesterol, and the level of HDL remained unchanged. The dynamics of these indicators in the treatment process is also presented in Fig. 1.

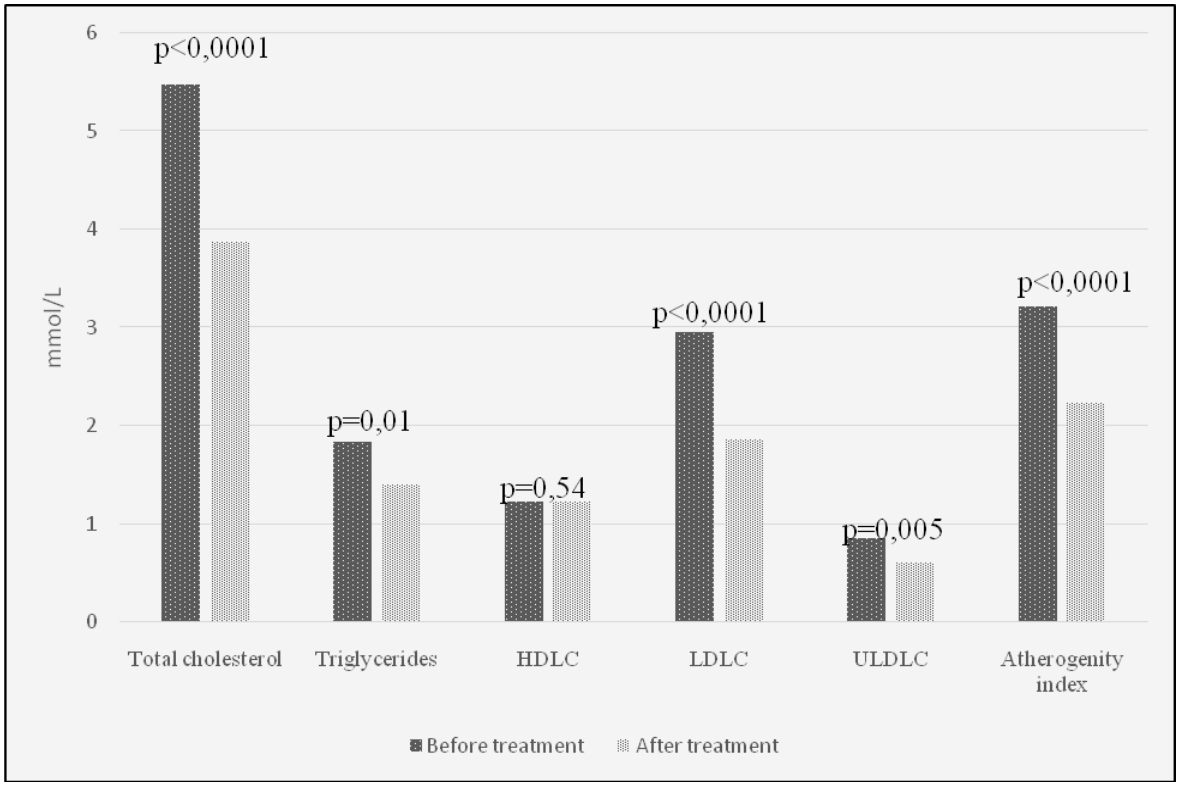

Figure 1. Dynamics of atherogenic lipid fractions after using complex therapy with rosuvastatin in patients with gout and hypertension

As seen from Figure 1, treatment with rosuvastatin resulted in a decrease in total cholesterol by 29,2% to 3,88 ± 0,78 mmol/L (p<0,0001), which corresponds to the normal level achieved at the end of the observation at 56, 67% of patients (n = 17). Earlier in the ASTEROID study, a more pronounced effect of rosuvastatin was observed, with a decrease in cholesterol by 33,8% [5], and a SATURN study showed a result of 27,98% [3] with a dose of 40 mg/day.

The level of triglycerides after therapy also showed a significant positive dynamics, dropping by 23,91% to 1,40 [1,12 – 1,94] mmol/L. In the previously noted randomized studies, a lower result was observed: -14,5% in the ASTEROID study and -6,25% in the SATURN study. As a result of treatment, normal parameters reached 63,3% of patients (n = 19) of the study group.

The main indicator of the proatherogenic blood potential– LDL – declinedmost significantly - by 36,95% to 1,86 ± 0,51 mmol/L (p<0,0001), normalizing in 86,67% of

patients (n = 26). The use of higher doses of rosuvastatin in randomized trials led to a decrease of 53,2% (ASTEROID) and 47,83% (SATURN), respectively.

The level of anti-atherogenic HDL after rosuvastatin therapy did not improve, remaining at a level of 1,23 mmol/L, which is lower than normal. In the past studies patients with CAD showed HDL-boosting effect of rosuvastatin - in the ASTEROID study it increased by 14,7%, and in the SATURN study by 11,26%. However, studying the effect of a 10 mg/day dose did not show such an effect [8], which coincides with our results. There is also evidence from individual authors that there is no effect of atorvastatin in a daily dose of 20 mg on HDL [14].

The Atherogenity index in patients of this group showed a significant normalization decreasing to 2,23 ± 0,83 ($p<0,0001$), decreasing by 30,53%. This was the result of a significant reduction in the level of proatherogenic LDL in the background of unchanged HDL.

Results of the study of biochemical inflammation activity indicators - ESR, C-RP, sialic acids, seromucoid, fibrinogen-A before and after treatment are presented in Table 2.

Table 2

Biochemical parameters of the patients with gout and arterial hypertension before and after standard therapy with rosuvastatin

Indicator	Target levels	Before treatment (n=30)	After treatment (n=30)	p
ESR, mm/h	1,0 – 10,0	21,70 ± 11,38	15,90 ± 9,33	<0,0001
C-RP, mg/mL	0,0 – 6,0	10,5 [0 – 12,0]	1,34 [0 – 6,0]	0,0007
Sialic acids, U	120,0 – 200,0	237,33 ± 95,66	202,33 ± 44,0	0,07
Seromucoid, U	3,0 – 5,0	5,78 ± 1,23	5,0 ± 1,25	0,004
Fibrinogen, g/L	2,0 – 4,0	5,66 ± 2,12	4,38 ± 1,64	0,002

The results show that after standard treatment with the addition of rosuvastatin all the inflammatory markers showed significant positive dynamics: ESR significantly decreased to 15,90 ± 9,33 mm/h ($p <0,0001$) not reaching normal levels, the level of C-RP reached a normal value of 1,34 [0 – 6,0] mg/ml ($p = 0,0007$), and the concentration of sialic acid and seromucoid decreased and reached the upper limit of the norm (202,33 ± 44,0 at $p=0,07$ and 5,0 ± 1,25 U at $p=0,004$ respectively). It should be emphasized that the normal values were reached only by the levels of C-RP, the other markers of inflammation did not show complete normalization: their mean values only approached the normal range. In our opinion, this can

be due to the persistence of inflammatory activity of a low degree, which is commonforpatients with moderate and severe gout. Additionally, our observation period could be not long enough for complete development of anti-inflammatory effect of studied treatment.

Conclusions:

The data shows that standard therapeutic complex with the addition of rosuvastatin at a dose of 10 mg/day leads to a statistically significant normalization of the average levels of total cholesterol, triglycerides, LDL and VLDL, causing no effect on the level of HDL. However, atherogenic index in these patients shows significant normalization.

Additionally, the treatment with rosuvastatin leads to significant normalization of the levels of C-RP, seromucoid and sialic acids, as well as statistically significant, but not reaching the normal values reduction of ESR and fibrinogen-A, indicating the anti-inflammatory effect of this therapeutic complex.

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